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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
KEMMERER, E	

18M1/1019

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ART UNIT	PAPER NUMBER
1812	5

DATE MAILED: 10/19/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire THREE (3) month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-23 are pending in the application.
   Of the above, claims 5-8 AND 10-23 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-4 AND 9 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-4 and 9, drawn to polypeptides and a therapeutic composition comprising same, classified in Class 530, subclass 399.

II. Claims 5-8, drawn to conjugates, classified in Class 524, subclass 20.

III. Claims 10-20, drawn to DNA, classified in Class 536, subclass 23.51.

IV. Claims 21-23, drawn to a method of treatment, classified in Class 514, subclass 12.

The inventions are distinct, each from the other because of the following reasons:

The polypeptides of Invention I are related to the conjugates of Invention II in that the conjugates comprise the polypeptides plus a toxin molecule. Although the polypeptides and conjugates are related in this way, they are distinct inventions because the polypeptides have a separate utility such as in raising diagnostic antibodies to the polypeptide, and the conjugates have a separate utility such as in cancer therapy.

The nucleic acids of Invention III are related to the protein of Invention I by virtue of encoding same. The DNA molecule has utility for the recombinant production of the protein in a host cell, as recited in claim 20. Although the DNA molecule and protein are related since the DNA encodes the

specifically claimed protein, they are distinct inventions because the protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from the natural source. Further, the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay.

Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the polypeptides of Invention I can be used in a materially different process, such as in raising diagnostic antibodies.

The DNA of Invention III is related to the conjugates of Invention II in that the DNA encodes the growth fragment factor component of the conjugates. However, the inventions are distinct because the conjugates can be made by another and materially different process, such as by synthetic peptide synthesis. Further, the DNA may be used for processes other than the production of the protein conjugates, such as nucleic acid hybridization assay.

Inventions II and IV are related as product and process of use. The inventions can be shown to be distinct if either or

both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the process for treating a hyperproliferative disease as recited in claims 22 and 23 can be can be practiced with a materially different product, such as chemotherapy agents or radiation.

Inventions III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the DNA of Invention III can be used in a materially different process, such as a probe in DNA hybridizations, and the process of Invention IV can be practiced with a materially different product, such as chemotherapy agents or radiation.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their recognized divergent subject matter, different classification, and separate search requirements, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Amy Collins on 7 October 1993, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-4 and 9. Affirmation of this election must be made by applicant in responding to this Office action. Claims 5-8 and 10-23 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

The application should be reviewed for typographical and grammatical errors. For example, the Accession Number is missing at page 34, line 19 and page 47, line 17. Also, Figure 4 is incorrectly referred to as Figure 5 at p. 38, line 22.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

The specification fails to teach a skilled artisan how to make and use KGF fragments or analogs exhibiting decreased cytotoxicity. Specifically, the specification provides no evidence that a keratinocyte growth factor (KGF) fragment (such

as $KGF_{des1-23}$) exhibits decreased cytotoxicity as compared to the mature, full-length KGF. The specification does provide evidence that $KGF_{des1-23}$ has increased mitogenic activity. However, it does not immediately follow from this data that $KGF_{des1-23}$ has decreased cytotoxicity. In fact, a skilled artisan might expect a more biologically active molecule to be more cytotoxic, in that an organism may not be able to support dramatically increased cell growth and division. In the absence of any guidance in the specification regarding decreased cytotoxicity of KGF fragments, a skilled artisan would be unable to make and use the invention as claimed, for example, in claim 4.

Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-3 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to $KGF_{des1-23}$. See M.P.E.P. §§ 706.03(n) and 706.03(z). The specification provides evidence that $KGF_{des1-23}$ exhibits increased mitogenic activity as compared to mature, full-length KGF. However, no other KGF fragments have been demonstrated to exhibit the increased mitogenic activity. In fact, other researchers have obtained KGF fragments lacking N-terminal sequences both shorter and longer than the disclosed $KGF_{des1-23}$, and have found that these KGF fragments display unchanged or lower mitogenic activity (see Ron et al., reference CC of record). This evidence

speaks to the high degree of unpredictability inherent in truncated growth factors. Thus, undue experimentation would be required by a skilled artisan to evaluate all non-exemplified KGF fragments for increased mitogenic activity, considering the lack of guidance in the specification regarding other truncated KGF's with increased mitogenic activity, and the high degree of unpredictability evident in the system.

Furthermore, no analogs of KGF fragments have been fully described or analyzed for biological activity. It is well known in the art that even minor changes in sequence can result in major changes in function, especially if the minor sequence change occurs within an active site or alters the overall conformation of the protein molecule. Thus, undue experimentation would be required by a skilled artisan to evaluate all non-exemplified analogs of KGF fragments that have increased mitogenic activity.

The claims are deemed to be free of the prior art. The closest prior art are cited here as of interest:

Ron et al., 1993, J. Biol. Chem. 268:2984-2988. (Reference CC of record).

Bellosta et al., 1993, J. Cell. Biol. 121:705-713. (Reference CA of record).

Ron et al. teach truncated forms of KGF which have either equal or lower mitogenic activity compared to the mature, full-

length KGF. The polypeptides are lacking N-terminal amino acid residues, including the glycosylation site in some instances. No truncated forms of KGF are disclosed which exhibit higher mitogenic activity compared to the mature, full-length KGF. Bellosta et al. disclose truncated K-FGF polypeptides lacking N-terminal amino acid residues which have increased biological activity. The truncated forms have lost the glycosylation site, similar to the truncated KGF disclosed in the instant application. However, in light of the report by Ron et al. that truncated KGF polypeptides lacking N-terminal amino acid residues including the glycosylation site have lower biological activity than the full-length KGF, Ron et al. effectively teaches away from the claimed invention.

No claims are allowed.

Specific inquiries concerning this communication should be directed to Elizabeth Kemmerer at (703) 308-2673. Inquiries of a general nature should be directed to the Group 180 secretary at (703) 308-0196. Papers related to this application may be submitted to Group 180 via facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November, 15, 1989). Papers should be faxed to the PTO Fax Center located in Crystal Mall 1 at (703) 305-3014.

ECK
Elizabeth C. Kemmerer, Ph.D.

October 15, 1993

ROBERT J. HILL, JR.
SUPERVISORY PATENT EXAMINER
GROUP 1800